

WHAT IS CLAIMED IS:

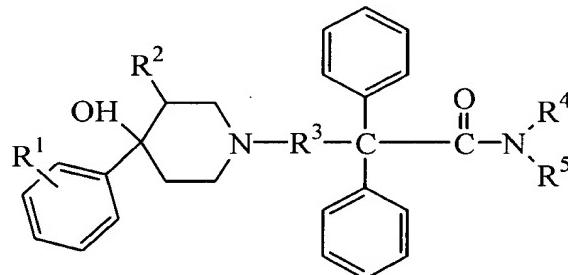
1 1. A pharmaceutical composition comprising:
2 a drug retained in a solid matrix in a manner causing release of said drug
3 from said solid matrix when said solid matrix is in the stomach,
4 said solid matrix when in the stomach being of a size large enough
5 to promote retention of said solid matrix in the stomach during the
6 fed mode, and

7 a fed mode inducing agent selected from the group consisting of:

- 8 (a) glycine, glycylglycine and salts thereof,
9 (b) C₄-C₈ sugar alcohols, L-1,3,4,5,6,7,8,9
10 (c) alkali and alkaline earth metal docusates,
11 (d) β -casomorphins, L-1,2,3
12 (e) dithioorganic acids of the formula L-1,2,3
 $\text{S}-\text{S}-(\text{CH}_2)_n-\text{CO}_2\text{H}$

13 in which n is 3 to 13,

14 (f) 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramides of the
15 formula



16 in which:

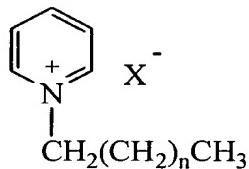
17 R¹ is a member selected from the group consisting of H,
18 lower alkyl, and halo,

19 R² is a member selected from the group consisting of H and
20 methyl,

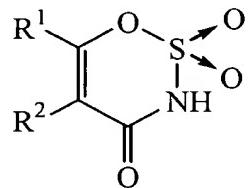
21 R³ is a member selected from the group consisting of —
22 CH₂CH₂— and —CH(CH₃)CH₂—,

23 R⁴ is lower alkyl, and

26 R⁵ is lower alkyl,
27 (g) arginine and arginine salts,
28 (h) the dipeptide Trp-Trp and salts thereof;
29 (i) alkyl pyridinium halides of the formula



- (j) dihydroxybenzoic acids, *Claim* 44
(k) stevioside,
(l) alkyl esters of N-L- α -aspartyl L-phenylalanine,
(m) aspartic acid and salts thereof, and
(n) 3,4-dihydro-1,2,3-oxathiazin-4-ones of the formula



in which R¹ and R² are independently selected from the group consisting of H and C₁-C₁₀ alkyl, and salts thereof in an amount that causes onset of the fed mode.

2. A pharmaceutical composition in accordance with claim 1 in which said fed mode inducing agent is retained in said solid matrix with said drug, said solid matrix causing release of both said fed mode reducing agent and said drug in a sustained manner.

1 3. A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent resides in a surface coating or layer on said solid matrix,
3 said surface coating or layer permitting substantially immediate release of said fed mode
4 reducing agent upon contact with gastric fluid while said solid matrix causes release of
5 said drug in a sustained manner.

1 A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is separate from said solid matrix, said solid matrix causing
3 release of drug in a sustained manner.

1 A pharmaceutical composition in accordance with claim 1 in which
2 the size of said solid matrix prior to ingestion is sufficiently large to promote retention of
3 said solid matrix in the stomach during the fed mode.

1 A pharmaceutical composition in accordance with claim 1 in which
2 said solid matrix swells or expands upon contact with gastric fluid to a size sufficiently
3 large to promote retention of said solid matrix in the stomach during the fed mode.

1 A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a member selected from the group consisting of glycine,
3 glycylglycine, and salts thereof.

1 A pharmaceutical composition in accordance with claim 7 in which
2 the amount of said fed mode inducing agent is from about 1 mg to about 500 mg.

1 A pharmaceutical composition in accordance with claim 7 in which
2 the amount of said fed mode inducing agent is from about 5 mg to about 150 mg.

1 A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a C₄-C₈ sugar alcohol.

1 A pharmaceutical composition in accordance with claim 10 in
2 which said C₄-C₈ sugar alcohol is xylitol.

1 A pharmaceutical composition in accordance with claim 10 in
2 which the amount of said C₄-C₈ sugar alcohol is from about 30 mg to about 1000 mg.

1 A pharmaceutical composition in accordance with claim 10 in
2 which the amount of said C₄-C₈ sugar alcohol is from about 100 mg to about 800 mg.

1 A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a member selected from the group consisting of alkali
3 and alkaline earth metal docusates.

1 **15.** A pharmaceutical composition in accordance with claim **14** in
2 which said fed mode inducing agent is a member selected from the group consisting of
3 calcium docusate and sodium docusate.

1 **16.** A pharmaceutical composition in accordance with claim **14** in
2 which said fed mode inducing agent is sodium docusate.

1 **17.** A pharmaceutical composition in accordance with claim **14** in
2 which the amount of said fed mode inducing agent is from about 30 mg to about
3 1000 mg.

1 **18.** A pharmaceutical composition in accordance with claim **14** in
2 which the amount of said fed mode inducing agent is from about 50 mg to about 400 mg.

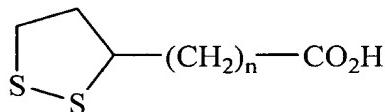
1 **19.** A pharmaceutical composition in accordance with claim **1** in which
2 said fed mode inducing agent is a β -casomorphin.

1 **20.** A pharmaceutical composition in accordance with claim **19** in
2 which said β -casomorphin is bovine β -casomorphin.

1 **21.** A pharmaceutical composition in accordance with claim **19** in
2 which the amount of said β -casomorphin is from about 1 mg to about 300 mg.

1 **22.** A pharmaceutical composition in accordance with claim **19** in
2 which the amount of said β -casomorphin is from about 5 mg to about 150 mg.

1 **23.** A pharmaceutical composition in accordance with claim **1** in which
2 said fed mode inducing agent is a dithioorganic acid of the formula



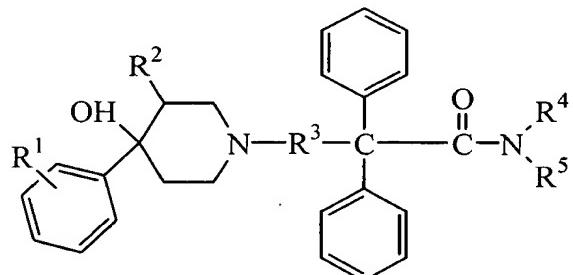
3 in which n is 3 to 13.

1 **24.** A pharmaceutical composition in accordance with claim **23** in
2 which said dithioorganic acid is α -lipoic acid.

1 **25.** A pharmaceutical composition in accordance with claim **23** in
2 which the amount of said dithioorganic acid is from about 30 mg to about 1000 mg.

1 **26.** A pharmaceutical composition in accordance with claim 23 in
2 which the amount of said dithioorganic acid is from about 40 mg to about 300 mg.

1 **27.** A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide
3 of the formula



4
5 in which:

6 R¹ is a member selected from the group consisting of H, lower alkyl, and
7 halo,

8 R² is a member selected from the group consisting of H and methyl,

9 R³ is a member selected from the group consisting of —CH₂CH₂— and
10 — CH(CH₃)CH₂—,

11 R⁴ is lower alkyl, and

12 R⁵ is lower alkyl.

1 **28.** A pharmaceutical composition in accordance with claim 27 in
2 which:

3 R¹ is a member selected from the group consisting of H, C₁-C₃ alkyl,
4 fluoro, and chloro,

5 R² is a member selected from the group consisting of H and methyl,

6 R³ is a member selected from the group consisting of —CH₂CH₂— and
7 — CH(CH₃)CH₂—,

8 R⁴ is C₁-C₃ alkyl, and

9 R⁵ is C₁-C₃ alkyl.

1 **29.** A pharmaceutical composition in accordance with claim 27 in
2 which R¹ is 4-chloro, R² is H, R³ is —CH₂CH₂—, R⁴ is CH₃, and R⁵ is CH₃.

1 **30.** A pharmaceutical composition in accordance with claim 27 in
2 which the amount of said 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from
3 about 0.5 mg to about 300 mg.

1 **31.** A pharmaceutical composition in accordance with claim 27 in
2 which the amount of said 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from
3 about 2 mg to about 15 mg.

1 **32.** A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a member selected from the group consisting of arginine
3 and arginine salts.

1 **33.** A pharmaceutical composition in accordance with claim 32 in
2 which the amount of said fed mode inducing agent is from about 3 mg to about 300 mg.

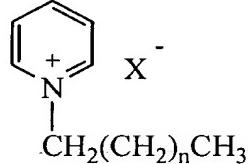
1 **34.** A pharmaceutical composition in accordance with claim 32 in
2 which the amount of said fed mode inducing agent is from about 30 mg to about 150 mg.

1 **35.** A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a member selected from the group consisting of the
3 dipeptide Trp-Trp and Trp-Trp salts.

1 **36.** A pharmaceutical composition in accordance with claim 35 in
2 which the amount of said Trp-Trp is from about 0.05 mg to about 300 mg.

1 **37.** A pharmaceutical composition in accordance with claim 35 in
2 which the amount of said Trp-Trp is from about 0.5 mg to about 10 mg.

1 **38.** A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is an alkyl pyridinium halide of the formula



3 in which n is 10 to 20 and X is halide.

- 1 **39.** A pharmaceutical composition in accordance with claim 38 in
2 which n is 12 to 16 and X is chloride.
- 1 **40.** A pharmaceutical composition in accordance with claim 38 in
2 which said alkyl pyridinium halide is cetyl pyridinium chloride.
- 1 **41.** A pharmaceutical composition in accordance with claim 38 in
2 which the amount of said alkyl pyridinium halide is from about 0.1 mg to about 200 mg.
- 1 **42.** A pharmaceutical composition in accordance with claim 38 in
2 which the amount of said alkyl pyridinium halide is from about 0.5 mg to about 50 mg.
- 1 **43.** A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a dihydroxybenzoic acid.
- 1 **44.** A pharmaceutical composition in accordance with claim 43 in
2 which said dihydroxybenzoic acid is gentisic acid.
- 1 **45.** A pharmaceutical composition in accordance with claim 43 in
2 which the amount of said dihydroxybenzoic acid is from about 3 mg to about 300 mg.
- 1 **46.** A pharmaceutical composition in accordance with claim 43 in
2 which the amount of said dihydroxybenzoic acid is from about 10 mg to about 100 mg.
- 1 **47.** A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is retained in said dosage form in such a manner that said
3 fed mode inducing agent is released substantially immediately into gastric fluid upon
4 contact of said dosage form with said gastric fluid while said drug is released into said
5 gastric fluid in a sustained manner by dissolution and diffusion of said drug out of said
6 solid matrix, by erosion or dissolution of said matrix, or by osmotic pressure within said
7 solid matrix.
- 1 **48.** A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is retained in said dosage form in such a manner that both
3 said drug and said fed mode inducing agent are released into gastric fluid in a sustained
4 manner by dissolution and diffusion of said drug and said fed mode inducing agent out of

5 said solid matrix, by erosion or dissolution of said matrix, or by osmotic pressure within
6 said solid matrix.

1 (49.) A pharmaceutical composition in accordance with claim 1 in which
2 said solid matrix is a member selected from the group consisting of cellulose polymers
3 and polyethylene oxide.

1 (50.) A pharmaceutical composition in accordance with claim 49 in
2 which said solid matrix is a member selected from the group consisting of
3 hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose,
4 hydroxypropylmethylcellulose, carboxymethylcellulose, and polyethylene oxide.

1 (51.) A pharmaceutical composition in accordance with claim 50 in
2 which said solid matrix is a member selected from the group consisting of
3 hydroxyethylcellulose, hydroxypropylcellulose, and polyethylene oxide.

1 (52.) A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is contained in a solid coating adhering to a surface of said
3 solid matrix.

1 (53.) A pharmaceutical composition in accordance with claim 52 in
2 which said solid coating is comprised of said fed mode inducing agent suspended in a
3 water-soluble matrix.

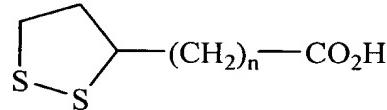
1 (54.) A pharmaceutical composition in accordance with claim 52 in
2 which said water-soluble matrix is a member selected from the group consisting of
3 cellulosics, vinyls, glycols and carbohydrates.

1 (55.) A pharmaceutical composition in accordance with claim 52 in
2 which said water-soluble matrix is a member selected from the group consisting of
3 sodium carboxymethylcellulose, sodium starch glycolate, crospovidone, microcrystalline
4 cellulose, lactose, and substituted hydroxypropylcellulose.

1 (56.) A method for pharmacologically inducing the fed mode in a
2 subject, said method comprising administering to said subject a fed mode inducing agent
3 selected from the group consisting of:

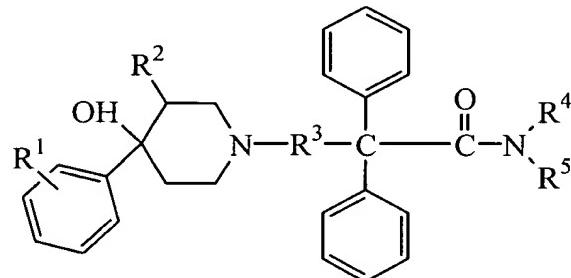
4 (a) glycine, glycylglycine and salts thereof,

- (b) C₄-C₈ sugar alcohols,
 - (c) alkali and alkaline earth metal docusates,
 - (d) β-casomorphins,
 - (e) dithioorganic acids of the formula



in which n is 3 to 13,

- (f) 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramides of the formula



in which:

R^1 is a member selected from the group consisting of H, lower alkyl, and halo,

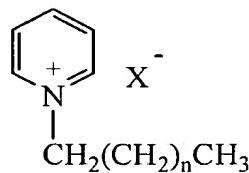
R^2 is a member selected from the group consisting of H and methyl,

R^3 is a member selected from the group consisting of —
 CH_2CH_2- and — $CH(CH_3)CH_2-$.

R^4 is lower alkyl, and

R⁵ is lower alkyl

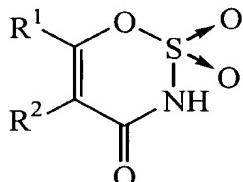
- (g) arginine and arginine salts,
 - (h) the dipeptide Trp-Trp and salts thereof;
 - (i) alkyl pyridinium halides of the formula



in which n is 10 to 20 and X is halide,

- (j) dihydroxybenzoic acids,

- 29 (k) stevioside,
30 (l) alkyl esters of N-L- α -aspartyl L-phenylalanine,
31 (m) aspartic acid and salts thereof, and
32 (n) 3,4-dihydro-1,2,3-oxathiazin-4-ones of the formula



in which R¹ and R² are independently selected from the group consisting of H and C₁-C₁₀ alkyl, and salts thereof, in an amount that causes onset of the fed mode.

1 **57.** A method in accordance with ~~claim 56~~ in which said fed mode
2 inducing agent is a member selected from the group consisting of glycine, glycylglycine,
3 and salts thereof.

58. A method in accordance with claim 57 in which the amount of said fed mode inducing agent is from about 1 mg to about 500 mg.

59. A method in accordance with claim 57 in which the amount of said fed mode inducing agent is from about 5 mg to about 150 mg.

1 **60.** A method in accordance with claim 56 in which said fed mode
2 inducing agent is a C₄-C₈ sugar alcohol. /

61. A method in accordance with claim 60 in which said C₄-C₈ sugar alcohol is xylitol.

62. A method in accordance with claim 60 in which the amount of said C₄-C₈ sugar alcohol is from about 30 mg to about 1000 mg.

1 **63.** A method in accordance with claim 60 in which the amount of said
2 C₄-C₈ sugar alcohol is from about 100 mg to about 800 mg.

1 **64.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a member selected from the group consisting of alkali and alkaline earth
3 metal docusates.

1 **65.** A method in accordance with claim 64 in which said fed mode
2 inducing agent is a member selected from the group consisting of calcium docusate and
3 sodium docusate.

1 **66.** A method in accordance with claim 64 in which said fed mode
2 inducing agent is sodium docusate.

1 **67.** A method in accordance with claim 64 in which the amount of said
2 fed mode inducing agent is from about 30 mg to about 1000 mg.

1 **68.** A method in accordance with claim 64 in which the amount of said
2 fed mode inducing agent is from about 60 mg to about 400 mg.

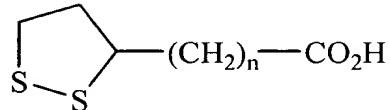
1 **69.** A method in accordance with claim 56 in which said fed mode
2 inducing agent is a β -casomorphin.

1 **70.** A method in accordance with claim 69 in which said
2 β -casomorphin is bovine β -casomorphin.

1 **71.** A method in accordance with claim 69 in which the amount of said
2 β -casomorphin is from about 1 mg to about 300 mg.

1 **72.** A method in accordance with claim 69 in which the amount of said
2 β -casomorphin is from about 5 mg to about 150 mg.

1 **73.** A method in accordance with claim 56 in which said fed mode
2 inducing agent is a dithioorganic acid of the formula



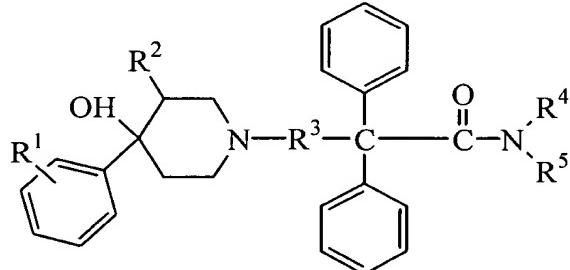
3 4 in which n is 3 to 13.

1 **74.** A method in accordance with claim 73 in which said dithioorganic
2 acid is α -lipoic acid.

1 **75.** A method in accordance with claim 73 in which the amount of said
2 dithioorganic acid is from about 30 mg to about 1000 mg.

1 **76.** A method in accordance with claim ~~73~~ in which the amount of said
2 dithioorganic acid is from about 40 mg to about 300 mg.

1 **77.** A method in accordance with claim ~~56~~ in which said fed mode
2 inducing agent is a 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide of the formula



3 in which:

4 R¹ is a member selected from the group consisting of H, lower alkyl, and
5 halo,

6 R² is a member selected from the group consisting of H and methyl,

7 R³ is a member selected from the group consisting of —CH₂CH₂— and
8 — CH(CH₃)CH₂—,

9 R⁴ is lower alkyl, and

10 R⁵ is lower alkyl.

1 **78.** A method in accordance with claim ~~77~~ in which:

2 R¹ is a member selected from the group consisting of H, C₁-C₃ alkyl,
3 fluoro, and chloro,

4 R² is a member selected from the group consisting of H and methyl,

5 R³ is a member selected from the group consisting of —CH₂CH₂— and
6 — CH(CH₃)CH₂—,

7 R⁴ is C₁-C₃ alkyl, and

8 R⁵ is C₁-C₃ alkyl.

1 **79.** A method in accordance with claim ~~77~~ in which R¹ is 4-chloro, R²
2 is H, R³ is —CH₂CH₂—, R⁴ is CH₃, and R⁵ is CH₃.

1 **80.** A method in accordance with claim ~~77~~ in which the amount of said
2 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from about 0.5 mg to about
3 300 mg.

1 **81.** A method in accordance with claim 77 in which the amount of said
2 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from about 2 mg to about 15 mg.

1 **82.** A method in accordance with claim 56 in which said fed mode
2 inducing agent is a member selected from the group consisting of arginine and arginine
3 salts.

1 **83.** A method in accordance with claim 82 in which the amount of said
2 fed mode inducing agent is from about 3 mg to about 300 mg.

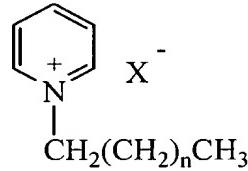
1 **84.** A method in accordance with claim 82 in which the amount of said
2 fed mode inducing agent is from about 30 mg to about 150 mg.

1 **85.** A method in accordance with claim 56 in which said fed mode
2 inducing agent is a member selected from the group consisting of the dipeptide Trp-Trp
3 and Trp-Trp salts.

1 **86.** An oral drug dosage form in accordance with claim 85 in which the
2 amount of said Trp-Trp is from about 0.05 mg to about 300 mg.

1 **87.** An oral drug dosage form in accordance with claim 85 in which the
2 amount of said Trp-Trp is from about 0.5 mg to about 10 mg.

1 **88.** A method in accordance with claim 56 in which said fed mode
2 inducing agent is an alkyl pyridinium halide of the formula



3
4 in which n is 10 to 20 and X is halide.

1 **89.** A method in accordance with claim 88 in which n is 12 to 16 and X
2 is chloride.

1 **90.** A method in accordance with claim 88 in which said alkyl
2 pyridinium halide is cetyl pyridinium chloride.

1 **91.** A method in accordance with claim **88** in which the amount of said
2 alkyl pyridinium halide is from about 0.1 mg to about 200 mg.

1 **92.** A method in accordance with claim **88** in which the amount of said
2 alkyl pyridinium halide is from about 0.5 mg to about 50 mg.

1 **93.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a dihydroxybenzoic acid.

1 **94.** A method in accordance with claim **93** in which said
2 dihydroxybenzoic acid is gentisic acid.

1 **95.** A method in accordance with claim **93** in which the amount of said
2 dihydroxybenzoic acid is from about 3 mg to about 300 mg.

1 **96.** A method in accordance with claim **93** in which the amount of said
2 dihydroxybenzoic acid is from about 10 mg to about 100 mg.

1 **97.** A pharmaceutical composition comprising:
2 a drug retained in a first solid matrix in a manner causing release of said
3 drug from first said solid matrix when said first solid matrix is in
4 the stomach, said solid first matrix when in the stomach being of a
5 size large enough to promote the retention of said first solid matrix
6 in the stomach during the fed mode, and
7 a pharmacological fed mode inducing agent active in inducing onset of the
8 fed mode, said fed mode inducing agent retained in a second solid
9 matrix configured to release said fed mode inducing agent into the
10 stomach in a sustained manner.

1 **98.** A pharmaceutical composition in accordance with claim **97** in
2 which said first solid matrix and said second solid matrix are a common single matrix.

1 **99.** A pharmaceutical composition in accordance with claim **97** in
2 which said fed mode inducing agent is sufficiently potent that onset of said fed mode
3 results from release of an amount of said fed mode inducing agent that is less than
4 500 mg.